Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial

*CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration**

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*See appendix for membership and contributions

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Summary

Background Venous thromboembolism is a common, potentially avoidable cause of death and morbidity in patients in hospital, including those with stroke. In surgical patients, intermittent pneumatic compression (IPC) reduces the risk of deep vein thrombosis (DVT), but no reliable evidence exists about its effectiveness in patients who have had a stroke. We assessed the effectiveness of IPC to reduce the risk of DVT in patients who have had a stroke.

Methods The CLOTS 3 trial is a multicentre parallel group randomised trial assessing IPC in immobile patients (ie, who cannot walk to the toilet without the help of another person) with acute stroke. We enrolled patients from day 0 to day 3 of admission and allocated them via a central randomisation system (ratio 1:1) to receive either IPC or no IPC. A technician who was masked to treatment allocation did a compression duplex ultrasound (CDU) of both legs at 7–10 days and, wherever practical, at 25–30 days after enrolment. Caregivers and patients were not masked to treatment assignment. Patients were followed up for 6 months to determine survival and later symptomatic venous thromboembolism. The primary outcome was a DVT in the proximal veins detected on a screening CDU or any symptomatic DVT in the proximal veins, confirmed on imaging, within 30 days of randomisation. Patients were analysed according to their treatment allocation. Trial registration: ISRCTN93529999.

Findings Between Dec 8, 2008, and Sept 6, 2012, 2876 patients were enrolled in 94 centres in the UK. The included patients were broadly representative of immobile stroke patients admitted to hospital and had a median age of 76 years (IQR 67–84). The primary outcome occurred in 122 (8·5%) of 1438 patients allocated IPC and 174 (12·1%) of 1438 patients allocated no IPC; an absolute reduction in risk of 3·6% (95% CI 1·4–5·8). Excluding the 323 patients who died before any primary outcome and 41 without any screening CDU, the adjusted OR for the comparison of 122 of 1267 patients *vs* 174 of 1245 patients was 0·65 (95% CI 0·51–0·84; p=0·001). Deaths in the treatment period occurred in 156 (11%) patients allocated IPC and 189 (13%) patients allocated no IPC died within the 30 days of treatment period (p=0·057); skin breaks on the legs were reported in 44 (3%) patients allocated IPC and in 20 (1%) patients allocated no IPC (p=0·002); falls with injury were reported in 33 (2%) patients in the IPC group and in 24 (2%) patients in the no-IPC group (p=0·221).

Interpretation IPC is an effective method of reducing the risk of DVT and possibly improving survival in a wide variety of patients who are immobile after stroke.

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Introduction

Venous thromboembolism is one of the most important, potentially preventable, causes of death and morbidity in patients in hospital.[1] Although its importance has long been recognised in patients undergoing surgery, it is now clear that medical patients (sometimes referred to as non-surgical patients) also have a high risk of venous thromboembolism. Patients who have had a stroke are at especially high risk; in prospective studies, venous thromboembolism has been detected in 20–42% of patients in hospital who have had a stroke.[2–4] Most healthcare systems in developed countries have established guidelines promoting routine assessments of risk of venous thromboembolism on hospital admission and the initiation of prophylaxis in high-risk patients.[5–7] Prophylaxis with antithrombotic drugs or physical methods, such as intermittent pneumatic compression (IPC), reduces the risks of deep vein thrombosis (DVT) in patients undergoing surgery; but the balance of risk and benefit for these approaches in medical patients is more contentious.[5,8,9] After stroke, graduated compression stockings are not effective, and the guideline-recommended strategy of selective use of anticoagulants in patients at high risk of venous thromboembolism and low risk of bleeding is impossible to achieve in practice because of the overlap of the factors that predict venous thromboembolism and those predicting bleeding risk.[3,10]

IPC includes inflatable sleeves that are wrapped around the legs and secured by Velcro (figure 1). The sleeves can be applied to the calf alone, or the calf and thigh. They are inflated, one side at a time, to compress the legs at intervals. Some types inflate sequentially, first distally, then proximally to increase venous flow. The frequency of inflation can be fixed, or in more sophisticated systems can be varied depending on the rate of venous refill. IPC is thought to reduce the risk of venous thrombosis by reducing stasis and stimulating release of intrinsic fibrinolytic factors.[11]

IPC has mainly been assessed in patients during, and immediately after, surgical operations. A systematic review[12] identified 22 randomised trials of IPC, which included a total of 2779 patients. Use of IPC was associated with a 64% reduction in the odds of DVT (proximal or calf; p<0·0001).[12] This review[12] concluded that a priority for future research was trials of "prevention of venous thromboembolism with mechanical methods among high-risk medical patients (such as those with stroke)". A Cochrane review[13] of trials of IPC after stroke identified only two trials including 177 patients in total,[13] showing IPC was associated with a non-significant reduction in risk of DVTs (OR 0·45, 95% CI 0·19–1·10).

The CLOTS 3 trial therefore aimed to establish whether the routine application of IPC to the legs of immobile patients who had had a stroke reduced their risk of DVT.

Methods

Study design and participants

CLOTS 3 trial is a multicentre, parallel group trial that took place in 105 hospitals in the UK. The protocol and statistical analysis plan have been published previously.[14,15] The full protocol can be viewed online.

To be included in the trial, patients had to be admitted to hospital within 3 days of acute stroke and be immobile (ie, could not mobilise to the toilet without the help of another person). Exclusion criteria included age lower than 16 years, subarachnoid haemorrhage, or contraindications to IPC such as dermatitis, leg ulcers, severe oedema, severe peripheral vascular disease, and congestive cardiac failure.

Patients or a proxy provided written informed consent. The protocol was approved by the Scotland A Multicentre Research Ethics Committee (08/MREC00/73) & the Newcastle & North Tyneside 1 Research Ethics Committee for England (08/H0906/137).

Randomisation and masking

On the day of admission (day 0) or up to day 3, patients were randomly assigned (ratio 1:1) to either receive IPC or not receive it. The clinician entered the patient's baseline data via a web-based or a 24-h telephone randomisation service. After checking the data for completeness and consistency, the system generated a treatment allocation. We used a minimisation algorithm to achieve optimum balance for the following factors: delay since stroke onset (day 0 or 1 *vs* day ≥2 days); stroke severity calculated with a validated prognostic model;[16] leg weakness (able or not to lift both legs off the bed); receiving heparin or warfarin at enrolment or had received thrombolysis since the stroke. Simple minimisation can theoretically lead to alternation of treatment allocation, which in this open treatment trial, might lead to fore-knowledge of the next treatment to be assigned. So, to ensure allocation concealment, our system also incorporated a degree of random allocation—ie, it allocated patients to the treatment group that minimised the difference between the groups with a probability of 0·8 rather than 1·0.[17]

All patients and investigators were aware of treatment allocation, the radiologist or technician doing the CDU were masked to treatment group.

Procedures

For patients allocated to the IPC group, we applied the Kendall SCD™ express sequential compression system (Covidien, MA, USA; figure 1), according to the manufacturer's instructions, to both legs. We used thigh-length sleeves. This system delivers sequential circumferential compression and incorporates venous refill technology so that the frequency of compression is tailored to the individual patient. We aimed to apply IPC continuously, both day and night, (except during washing, physiotherapy, or screening compression duplex ultrasound [CDUs]) for a minimum of 30 days from randomisation, or until a second screening CDU had been done (if after 30 days). IPC was discontinued early if the patient: became independently mobile, was discharged from the participating hospital, declined to continue IPC, had adverse effects of the IPC that warranted removal. To enhance adherence, the manufacturer introduced a modified IPC sleeve, the Kendall SCD™ sequential compression "Comfort" sleeves. We switched to this new sleeve for the 1197 (42%) patients

For the **study protocol** see http://www.clotstrial.com

Figure 1: **The Kendall SCD™ express sequential compression system (Covidien, MA, USA) with Comfort sleeves applied to a patient's legs**

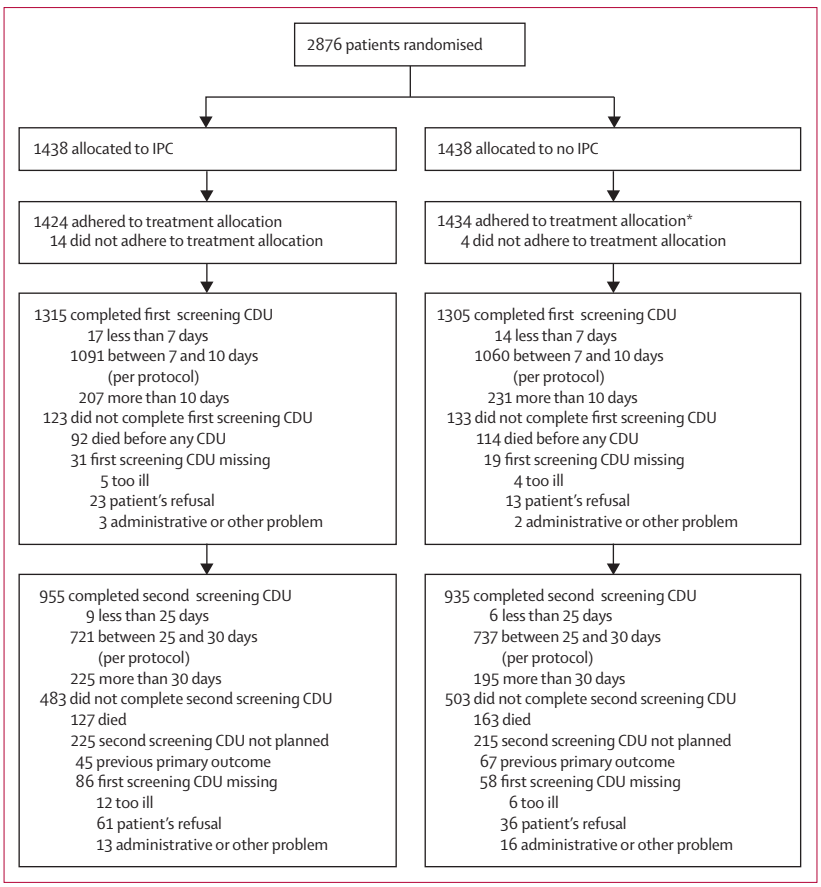

Figure 2: **Trial profile**
CDU=compression duplex ultrasound. IPC=intermittent pneumatic compression. *Four patients allocated avoid IPC received some IPC: three were transferred to an intensive therapy unit or high dependency unit where IPC was standard of care; the other patient received IPC because of miscommunication of the treatment allocation, which resulted in 3 days' treatment with IPC.

recruited after Oct 17, 2011. Nursing staff recorded the application of IPC on the medication chart every day to aid adherence monitoring. We defined perfect adherence (ie, 100% adherence) as wearing IPC from randomisation until the patient regained mobility, was discharged from a participating hospital, died, or until 30 days or until a delayed second screening CDU. We asked that clinicians should not take the patient's treatment allocation into account when deciding whether or not to use antithrombotic drugs after enrolment, to ensure that, as far as possible, both treatment groups received the same background thromboprophylactic care.

For the follow-up, we aimed to do a CDU between days 7 and 10 and, wherever practical, between days 25 and 30 after randomisation, even if the patient had been discharged from hospital. The plan not to do the second CDU was captured securely before randomisation, which might be the case if the patient was likely to be discharged home to another region or transferred to a rehabilitation facility that did not have facilities to do a CDU, and was remote from the randomising centre. We allowed researchers to plan not to do a second CDU to minimise bias that might arise because of unplanned failures to complete a second CDU. We stipulated that; the IPC should be removed before the CDU, to mask the radiologist or technician to the treatment group; the technician should be performing CDU regularly as part of a clinical service and the CDU should cover at least the popliteal and femoral veins in both legs (ie, visualisation of calf veins was not mandatory). The technician completed a report form including: whether there was a DVT affecting femoral, popliteal or calf veins in each leg; whether the calf veins were fully visualised; whether the patient arrived wearing IPC. We obtained a hard copy of any scans reporting a primary outcome for central verification by a radiologist (JR). In the absence of a hard copy we obtained the local clinical radiology report of the CDU.

After discharge, or death in hospital, based on a review of the medication charts and medical records, the local coordinator completed a discharge form that included the early secondary outcomes. We sent a postal questionnaire to every patient's general practitioner about 24 weeks after enrolment to establish the patient's vital status, and the occurrence of DVTs or pulmonary emboli since hospital discharge. We followed up surviving patients at 6 months after enrolment by postal questionnaire; in non-responders, the chief investigator (MD) did a telephone interview masked to treatment allocation.

Statistical analysis

The primary outcome was a symptomatic or asymptomatic DVT in the popliteal or femoral (proximal) veins detected on a screening CDU or any symptomatic DVT in the popliteal or femoral veins, confirmed on imaging, within 30 days of randomisation.

The secondary outcomes within 30 days were: death, any DVT (including symptomatic or asymptomatic calf, popliteal or femoral), symptomatic DVT, pulmonary embolism confirmed on imaging or autopsy, complications of IPC (eg, skin breaks, falls with injury, fractures) and adherence. For every patient, we expressed adherence as a percentage, which we calculated from the number of days the IPC was worn (ie, end date minus start date) divided by the number of days it should have been worn according to our protocol. We did not collect the number of hours per day the IPC was worn.

The secondary outcomes at 6 months were: death from any cause and any confirmed symptomatic or asymptomatic DVT or pulmonary embolism occurring since randomisation. Other secondary outcomes measured at 6 months included: place of residence; functional status and health related quality of life and symptoms of possible post phlebitic leg syndrome (eg, leg swelling or ulcers). These data will be reported elsewhere as part of a health economic analysis.

We originally planned to enrol at least 2000 patients, although we prespecified that the trial steering committee would review this in the light of the overall rate of

the primary outcome in both groups combined. This aimed to give the trial more than 90% power (α 0·05 [2-sided]) to identify an absolute reduction of risk of our primary outcome of 4% (ie, from 10% to 6%). On Nov 1, 2010, the frequency of the primary outcome in both groups combined among the 581 patients enrolled was 12·2%. The trial steering committee, without reference to the unblinded data therefore revised the sample size to 2800 to ensure that the trial maintained power to detect a 4% absolute difference in proximal DVT (ie, 14% to 10%). The frequency of the primary outcome later fell gradually but the trial steering committee decided not to reduce the sample size. The trial steering committee remained masked to any analyses split by treatment group throughout the trial.

The trial statistician (CG) prepared analyses of the accumulating data, which the independent data monitoring committee reviewed in strict confidence at least once a year. No explicit stopping rules existed. No other members of the trial team, trial steering committee, or participants had access to these analyses. Before recruitment was completed, and without input from the trial statistician or reference to the unblinded data, the trial steering committee prepared a detailed analysis plan that was then published.[15] For the purposes of all primary analyses, we retained participants in the treatment group to which they were originally assigned irrespective of the treatment they actually received. Inevitably, some patients withdrew and were lost to follow-up, and some who did return follow-up questionnaires left items blank. We excluded these patients from the analyses that they had no data for, and we did sensitivity analyses to assess the effect of these exclusions on the overall conclusions. For binary outcomes (eg, occurrence of a primary outcome or not), outcomes are presented as odds ratios (ORs) and 95% CIs, adjusted using logistic regression for the variables in the minimisation algorithm. We calculated absolute reductions in risk from these values. We used Cox proportional hazards modelling to analyse the effect of treatment on survival to 6 months, adjusting for the variables included in our minimisation algorithm.

The prespecified subgroup analyses were: the effect of treatment allocation on the primary outcome subdivided by key baseline variables: delay from stroke onset to randomisation (day 0 or 1 *vs* day 2 to 7 and day 0 to 2 *vs* 3–7); weakness of the legs (able to lift both legs or not); stroke severity (with a validated prognostic model);[16] risk of DVT (high *vs* low; based on presence or not of risk factors at baseline);[18] use of heparin, warfarin, or thrombolysis at the time of enrolment; type of stroke (confirmed haemorrhagic *vs* ischaemic stroke or unknown pathological type of stroke); type of compression sleeves used (Original *vs* Comfort). We did the subgroup analyses by observing the change in log-likelihood when the interaction between the treatment and the subgroup was added into a logistic regression model. We did the statistical analyses using SAS v 9.2 (SAS Institute Inc, Cary, NC, USA).

The study is registered with http://www.Controlled-Trials.com, number ISRCTN93529999.

Role of the funding source

The funding organisations, including Covidien, had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding

	IPC (n=1438)	No IPC (n=1438)
Age (years)		
Median (IQR)*	76 (67–83)	77 (68–84)
Mean age (SD)	74·2 (12·3)	74·9 (11·9)
Sex		
Male	695 (48%)	688 (48%)
Final diagnosis at hospital discharge		
Stroke or TIA (definite or probably ischaemic)	1211 (84%)	1217 (85%)
Confirmed haemorrhagic stroke	187 (13%)	189 (13%)
Unknown type	19 (1%)	14 (1%)
Non strokes (included in primary analysis)	19 (1%)	18 (1%)
Missing (no discharge form)	2 (<1%)	0
Past history and risk factors		
Previous deep vein thrombosis or pulmonary embolism	66 (5%)	74 (5%)
Diabetes mellitus	256 (18%)	247 (17%)
Peripheral vascular disease	24 (2%)	31 (2%)
Overweight	417 (29%)	457 (32%)
Current cigarette smoker	250 (17%)	228 (16%)
Independent in daily activities before stroke*	1301 (90%)	1295 (90%)
Lives alone before stroke*	500 (35%)	503 (35%)
Indicators of stroke severity		
Able to lift both arms off bed*	499 (35%)	502 (35%)
Able to talk and orientated in time, place, and person*	886 (62%)	845 (59%)
Able to lift both legs off bed†	494 (34%)	493 (34%)
Able to walk without help*	0	0
Stroke severity—probability of being alive and independent in daily activities=0–0·15)†	898 (62%)	892 (62%)
Stroke severity—median (IQR) probability of being alive and independent in daily activities	0·09 (0·02–0·31)	0·09 (0·01–0·31)
On warfarin at recruitment	25 (2%)	29 (2%)
On heparin at recruitment	86 (6%)	78 (5%)
Taken aspirin, dipyridamole, or clopidogrel in past 24 h at recruitment	970 (67%)	971 (68%)
Received thrombolysis since admission	249 (17%)	255 (18%)
On heparin or warfarin at recruitment or received thrombolysis since admission†	347 (24%)	352 (24%)
Delay		
Delay since stroke onset to randomisation=0–1 days†	624 (43%)	620 (43%)
Delay since stroke onset to randomisation=2 days†	478 (33%)	457 (32%)
Delay since stroke onset to randomisation ≥3 days†	336 (23%)	361 (25%)
Compression duplex ultrasound at 25–30 days deemed unlikely to be practical at time of randomisation	225 (16%)	215 (15%)

Data are number of patients (%) unless otherwise stated. IPC=intermittent pneumatic compression. TIA=transient ischaemic attack. *Factors included in model to predict probability of being alive and independent at 6 months.[16] †Variables included in minimisation.

Table 1: **Baseline characteristics of patients enrolled into the CLOTS 3 trial (N=2876)**

	IPC group	No IPC group
30-day clinical outcomes and background treatment		
Discharge form received (after hospital discharge or death)	1436 (99·9%)	1438 (100%)
Vital status at 30 days known	1432	1431
Post-randomisation prophylactic dose heparin/LMWH prescribed	248 (17%)	240 (17%)
Post-randomisation treatment dose heparin/LMWH prescribed	182 (13%)	219 (15%)
Graduated compression stockings worn	118 (8%)	42 (3%)
Thigh-length stockings only	90 (6%)	22 (2%)
Below-knee graduated compression stockings worn only	17 (1%)	19 (1%)
Both long and short worn	10 (<1%)	1 (<1%)
Unknown length	1 (<1%)	0
6-month clinical outcomes		
Patient or proxy withdrew consent before 6 months	13 (<1%)	7 (<1%)
Missing 6 month follow-up	10 (<1%)	13 (<1%)
No follow-up form because patient dead	330 (23%)	367 (26%)
Follow-up form received	1098 (76%)	1058 (74%)

IPC=intermittent pneumatic compression. LMWH=low-molecular-weight heparin.

Table 2: **Patients' clinical outcomes**

author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 8, 2008, and Sept 6, 2012, 2876 patients were enrolled in 94 centres in the UK and an additional 11 centres took responsibility for delivering the allocated treatment and follow-up for patients who were transferred from the randomising hospital (appendix). Of the 2876 patients enrolled, 1438 were randomly assigned to receive IPC and 1438 to receive no IPC (figure 2). The patients' baseline characteristics were well balanced between treatment groups (table 1). Use of prophylactic dose heparin or low molecular weight (LMWH) after randomisation was very similar between treatment groups (table 2). There was a small excess of the use of graduated compression stockings in the IPC group, perhaps because manufacturers have previously recommended using IPC and graduated compression stockings in combination.

The mean duration of IPC use was 12·5 days (SD 10·9) and the median duration was 9 days (IQR 3–22). Perfect adherence was achieved in 445 (31%) of 1438 patients in the IPC group. The mean adherence was 59·2% (SD 10·9) and the median adherence was 65·4% (IQR 20–100).

Table 3 shows patients' outcomes with respect to our primary and secondary outcomes within 30 days of enrolment. The primary outcome occurred in 122 (8·5%) of 1438 patients allocated to IPC and in 174 (12·1%) of 1438 patients allocated to no IPC (table 3; OR 0·65 (95% CI 0·51–0·84; p=0·001 after adjustment for baseline variables). The absolute reduction risk (ARR) was 3·6% (95% CI 1·4–5·8%). 156 (5%) of 2876 patients attended their first or second CDU wearing IPC sleeves, which meant that the technician could not be masked for their assessment. Our primary outcome was confirmed in 276 (93%) of the 296 patients by central review of the images (reviewed by JR) and in the remaining 20 (7%) patients by the local clinical report. To allow for any observer bias in detecting symptomatic DVTs not detected on routine screening CDU, we repeated the primary analysis excluding those primary outcomes where a DVT was suspected before the CDU (n=22). The estimates of effect were unchanged (data not shown).

We noted significant reductions in the outcome of any DVT(symptomatic or asymptomatic involving proximal or calf veins) and symptomatic DVT (including proximal or calf; table 3). Not all patients had their calf veins visualised fully, so in patients with a first CDU, we are unable to exclude an isolated calf DVT in 615 (47%) of 1315 patients in the IPC group and in 596 (46%) of 1305 patients in the no-IPC group. In those with a second CDU, we are unable to exclude an isolated calf DVT in 453 (47%) of 955 patients in the IPC group and in 458 (49%) of 938 patients in the non-IPC group.

Patients allocated to IPC had significantly more skin breaks than did patients allocated to no IPC but the risk of falls with injury or fractures within 30 days did not differ between groups (table 3). Few of the skins breaks or falls with injury were attributed by the local researchers to the IPC. Most adverse events either occurred when IPC had been removed, or skin breaks affected the heels (which are not covered by the IPC sleeves) so were unlikely to be due to the IPC. However, the reporting of secondary outcomes in hospital and adverse effects was based on case-note review and was not masked to treatment allocation. These data for adverse events are therefore prone to ascertainment bias.

We noted non-significantly fewer deaths from all causes within 30 days for those allocated IPC (table 3). The Cox model adjusted for the factors included in our minimisation algorithm showed a reduced probability of death for death up to 6 months after randomisation in those allocated IPC (figure 3).

We noted no evidence of an excess of venous thromboembolism events in the post treatment period to indicate that IPC simply deferred venous thromboembolism events (table 4). In our prespecified subgroup analyses, we noted no significant interactions in our subgroups with the effect of treatment on the primary outcome (figure 4).

Discussion

The CLOTS 3 trial has shown that IPC (delivering sequential circumferential compression via thigh-length sleeves at a frequency determined by the venous refill time) applied to immobile stroke patients, is safe, and reduces the risk of proximal DVT (our primary outcome), symptomatic DVTs (proximal or calf) and all DVTs (symptomatic or asymptomatic, proximal or calf). The reduction in symptomatic proximal DVTs was not

	IPC (n=1438)	No IPC (n=1438)	Absolute risk difference (95% CI)	Risk ratio (95% CI)*	Odds ratio (95% CI)	p value
Primary outcome						
Primary outcome (proximal DVT)	122 (8·5%)	174 (12·1%)	−3·6 (−5·8 to −1·4)			
Alive and free of primary outcome	1145 (79·6%)	1071 (74·5%)				
Died before any primary outcome	147 (10·2%)	176 (12·2%)				
Missing	24 (1·7%)	17 (1·2%)				
Unadjusted (dead and missing patients excluded)	122/1267 (9·6%)	174/1245 (14·0%)	−4·3 (−6·9 to −1·8)	0·69 (0·55 to 0·86)	0·66 (0·51 to 0·84)	0·001
Primary analysis–adjusted (dead and missing patients excluded)				0·68 (0·54 to 0·85)	0·65 (0·51 to 0·84)	0·001
Unadjusted (dead patients included with DVT and missing patients included with no DVT)	269/1438 (18·7%)	350/1438 (24·3%)	−5·6 (−8·6 to −2·6)	0·77 (0·67 to 0·89)	0·71 (0·59 to 0·85)	0·00023
Adjusted (dead patients included with DVT and missing patients included with no DVT)				0·75 (0·64 to 0·88)	0·71 (0·60 to 0·86)	0·00021
Secondary outcomes by 30 days or later second compression duplex ultrasound						
Dead by 30 days	156 (10·8%)	189 (13·1%)	−2·3 (−4·7 to 0·1)	0·82 (0·66 to 1·01)	0·80 (0·63 to 1·01)	0·057
Symptomatic proximal DVT	39 (2·7%)	49 (3·4%)	−0·7 (−2·0 to 0·6)	0·79 (0·52 to 1·20)	0·79 (0·51 to 1·21)	0·269
Asymptomatic proximal DVT	83 (5·8%)	125 (8·7%)	−2·9 (−4·8 to −1·0)	0·66 (0·50 to 0·87)	0·65 (0·48 to 0·86)	0·003
Symptomatic DVT (proximal or calf)	66 (4·6%)	90 (6·3%)	−1·7 (−3·3 to −0·0)	0·73 (0·53 to 0·99)	0·72 (0·52 to 0·99)	0·045
Any DVT (symptomatic or asymptomatic, proximal or calf)	233 (16·2%)	304 (21·1%)	−4·9 (−7·8 to −2·1)	0·76 (0·64 to 0·89)	0·72 (0·60 to 0·87)	0·001
All confirmed pulmonary embolism (imaging or autopsy)	29 (2·0%)	35 (2·4%)	−0·4 (−1·5 to 0·7)	0·83 (0·51 to 1·35)	0·83 (0·50 to 1·36)	0·453
Any DVT or confirmed pulmonary embolism	248 (17·2%)	325 (22·6%)	−5·4 (−8·3 to −2·4)	0·75 (0·64 to 0·88)	0·72 (0·59 to 0·86)	0·00035
Any DVT or death	377 (26·2%)	472 (32·8%)	−6·6 (−9·9 to −3·3)	0·78 (0·68 to 0·88)	0·72 (0·61 to 0·85)	<0·0001
Any DVT, pulmonary embolism, or death	391 (27·2%)	491 (34·1%)	−7·0 (−10·3 to −3·6)	0·78 (0·68 to 0·88)	0·72 (0·61 to 0·84)	<0·0001
Potential adverse effects of IPC						
Skin breaks	44 (3·1%)	20 (1·4%)	1·7 (0·6 to 2·7)	2·15 (1·30 to 3·50)	2·23 (1·31 to 3·81)	0·002
Skin breaks attributed to IPC	10 (0·7%)	0 (0·0%)	0·7 (0·3 to 1·1)			
Lower limb ischaemia or amputation	0 (0·0)	2 (0·1%)	−0·1 (−0·3 to 0·1)			
Falls with injury in 30 days	33 (2·3%)	24 (1·7%)	0·6 (−0·4 to 1·6)	1·38 (0·82 to 2·29)	1·39 (0·82 to 2·37)	0·221
Falls with injury in 30 days attributed to IPC	1 (0·1%)	0 (0·0)	0·1 (−0·1 to 0·2)			
Fractures within 30 days	4 (0·3%)	4 (0·3%)	0·0 (−0·4 to 0·4)			

All odds ratios and risk ratios are adjusted for the variables included in the minimisation algorithm, as specified in the statistical analysis plan, unless otherwise stated. IPC=intermittent pneumatic compression. DVT=deep vein thrombosis. *Risk ratios were not prespecified in our statistical analysis plan but are presented to enhance interpretation of results.

Table 3: **Primary and secondary outcomes within 30 days of randomisation**

significant. Although we noted a significant excess of skin breaks and a non-significant excess of falls with injury, the absolute risks were low and most adverse events were not attributed to the IPC. Reassuringly, there was a potentially important improvement in survival.

The CLOTS 3 trial included about the same number of patients as had been included in all previous randomised trials combined in medical and surgical patients of IPC identified by systematic reviews (panel).[8,12,13] The CLOTS 3 trial focused on prevention and identification of proximal DVTs, which are detected more reliably with CDU, and are considered clinically more important than DVTs restricted to the calf. Calf DVT's are the most frequent component of the cluster of venous thromboembolism events used in previous trials of venous thromboembolism prophylaxis,[8,19] yet their detection with CDU is technically challenging and results are inconsistent. The patients in CLOTS 3 were enrolled by many hospitals in the UK, and had baseline characteristics that were similar to the 47% of unselected patients with acute stroke admitted to Scottish hospitals

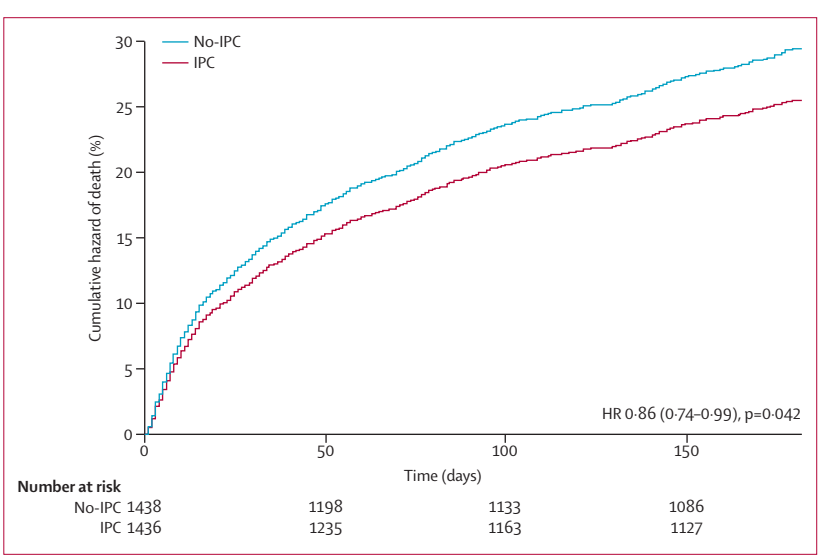

Figure 3: **Cumulative hazard of death during the 6 months after randomisation in the two treatment groups**
IPC=intermittent pneumatic compression. Note that two patients in the IPC arm withdrew very early, did not have a date of withdrawal or death and are therefore not included in the baseline number at risk.

	IPC (n=1438)	No IPC (n=1438)	Absolute risk difference (95% CI)	Risk ratio (95% CI)*	Odds ratio (95% CI)	p value
Dead by 6 months	320 (22·3%)	361 (25·1%)	−2·9 (−6·0 to 0·3)	0·87 (0·75 to 1·00)	0·85 (0·70 to 1·01)	0·059
Any DVT	240 (16·7%)	312 (21·7%)	−5·0 (−7·9 to −2·1)	0·76 (0·64 to 0·89)	0·72 (0·60 to 0·87)	0·001
Any symptomatic DVT	77 (5·4%)	101 (7·0%)	−1·7 (−3·4 to 0·1)	0·76 (0·56 to 1·01)	0·75 (0·55 to 1·02)	0·061
Any confirmed PE	42 (2·9%)	49 (3·4%)	−0·5 (−1·8 to 0·8)	0·86 (0·57 to 1·29)	0·86 (0·56 to 1·30)	0·463
Any death, DVT, or PE	526 (36·6%)	626 (43·5%)	−7·0 (−10·5 to −3·4)	0·83 (0·75 to 0·92)	0·74 (0·63 to 0·86)	<0·0001

Odds ratios and risk ratios are adjusted for factors included in our minimisation algorithm, as specified in the statistical analysis plan. IPC=intermittent pneumatic compression. DVT=deep vein thrombosis. PE=pulmonary embolism. *Risk ratios were not prespecified in our statistical analysis plan but are presented to enhance interpretation of results.

Table 4: **All deaths and venous thromboembolic events (including those in first 30 days) during the 6-month follow-up**

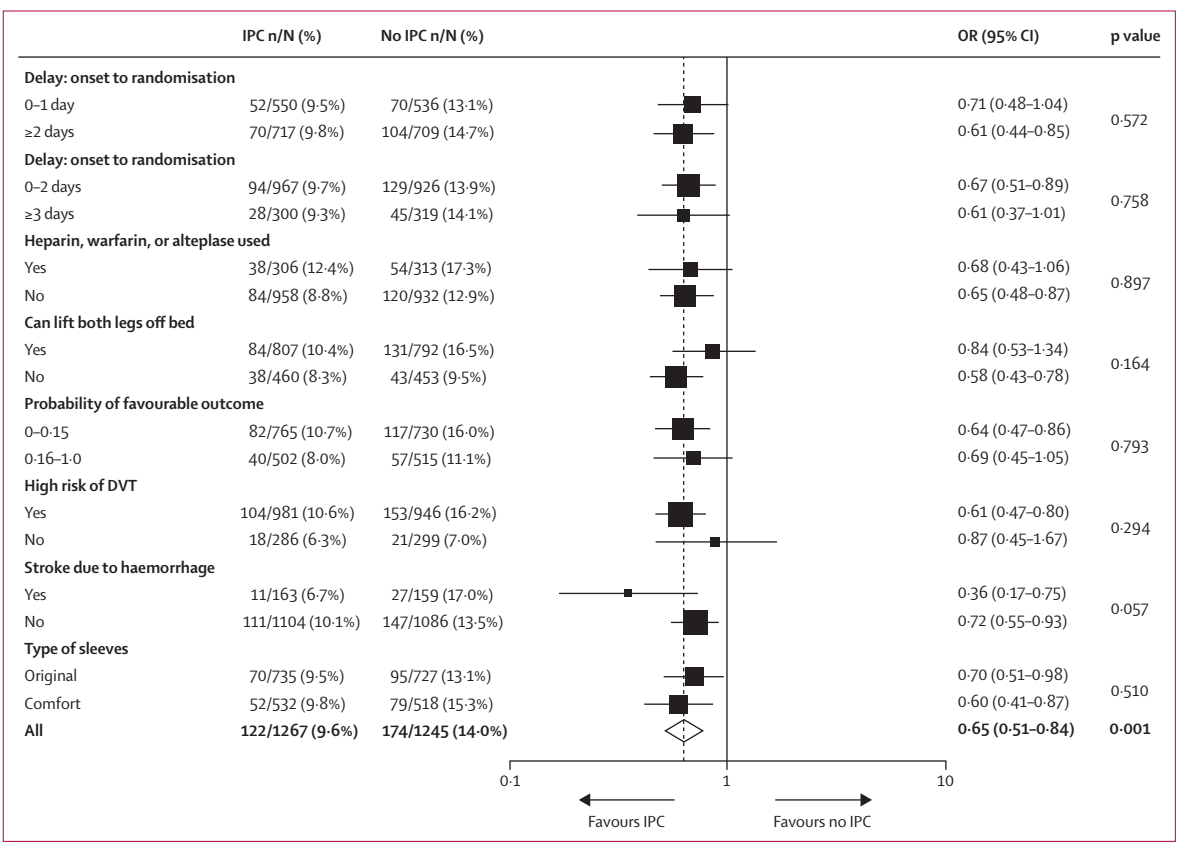

Figure 4: **Frequency of the primary outcome by allocated treatment in the prespecified subgroups**
The graph show the point estimates of the OR (adjusted for baseline factors) for every subgroup as a square (whose size is proportional to the amount of information) and the horizontal lines depict the 95% CIs. The open diamond indicates the adjusted ORs with 95% CIs for all patients enrolled. The vertical line, at the OR of unity corresponds to the line of no effect. OR values of less than unity correspond to a reduction in the primary outcome with IPC. p values are for the interaction between the treatment effect and the subgroup. Patients who died without previous DVT (n=323) and those without either CDU (n=41) are excluded from the denominators, which are therefore different to the total number allocated to each treatment group. IPC=intermittent pneumatic compression. DVT=deep vein thrombosis. CDU=compression duplex ultrasound. OR=odds ratio.

who were initially immobile (unpublished data from the Scottish Stroke Care Audit).[20] This suggests that our results have external validity and would apply to about half of all patients who had had a stroke admitted to hospital. Our prespecified decision to increase our sample size to take account of the overall primary event rate ensured that the trial had adequate power (>90%) to detect a 4% absolute difference in risk of proximal DVT. Central randomisation, mainly masked assessment of our primary outcome, low losses to follow-up and intention-to-treat analysis have minimised bias.

The trial has some limitations: moderate adherence to IPC; imperfect masking of the technicians (because of some patients attending the CDU wearing the IPC, which could bias detection of our primary outcome); no masking of caregivers (which might bias their use of background treatment and assessment of some of the secondary outcomes); no masking of patients; some scheduled CDUs

did not include the calf veins and some were missing; and, we did not systematically screen for pulmonary emboli. All of these might mean we have underestimated the frequency of venous thromboembolism. Furthermore, because we systematically screened for them, many patients found to have asymptomatic DVT were then treated with anti-coagulants to lessen the risk of symptomatic events (DVTs, pulmonary emboli, and deaths) occurring. This might bias the estimate of the effect of IPC. Other potential limitations included: lack of central verification of negative scans, use of selective source data verification and imbalance in the background use of graduated compression stockings but we deem these are unlikely to have introduced bias or altered the external validity of the results.

The search strategy used in the Cochrane review of physical methods for preventing deep vein thrombosis in stroke was updated in March 2013.[13] Only the two small randomised trials included in the original review were identified. When the results of CLOTS 3 are incorporated the estimates of treatment effects are an OR of 0·66 (95% CI 0·52–0·84) for proximal DVT, an OR of 0·71 (0·59–0·85) for any DVT and an OR of 0·81 (0·65–1·01) for deaths by the end of the treatment period. The two other trials did not report any symptomatic DVTs or pulmonary emboli.

The reduction in DVT observed in CLOTS 3 is likely to be due to the reduced venous stasis and possibly the effects on intrinsic fibrinolysis observed with IPC.[11] The improved survival to 6 months observed in those allocated IPC is potentially of clinical significance. However, the effect on survival was not expected, and the CLOTS 3 trial had less than 50% power to detect such an effect; a trial with about 8500 patients would be required to provide 90% power to detect the observed reduction in all-cause mortality. Unfortunately, the autopsy rate was very low, so we were unable reliably to assign a cause to most deaths, especially given the difficulty of distinguishing pulmonary embolism from other cardio-respiratory problems in patients who have had a stroke.[21] Selection bias and ascertainment biases are unlikely explanations for our findings since prognostic factors were balanced at baseline and losses to follow-up were extremely low. Therefore, taken with the pattern of benefits across all the secondary outcomes, it seems plausible that the difference in survival might be real and attributable, at least in part, to IPC. The most likely mechanism is a reduction in undiagnosed pulmonary embolism that contributed to death.

Previous meta-analyses of trials of heparins/LMWH in medical patients, including those with stroke (n=36 122 patients) have shown significant reductions in pulmonary emboli (three in 1000, 95% CI 1–3), but only non-significant reduction in deaths (six in 1000, 0–11), perhaps partly because any reduction in major venous thromboembolism was offset by a significant increase in major bleeds (four in 1000, 1–7).[8,9] By contrast, IPC was not associated with an excess of any major adverse effects that might offset the benefits. The observed effect of IPC on survival in CLOTS 3 is also reassuring about its safety in this high-risk vulnerable population.

CLOTS 3 provides clear evidence that IPC is effective in reducing the risk of both proximal, symptomatic and "any DVT" in immobile patients who have had a stroke. Our subgroup analyses suggest that the effect is similar across a broad range of patients. Importantly, IPC seems to be as effective in patients with haemorrhagic stroke (figure 4). Moreover, we have shown that IPC is moderately well tolerated and might even improve survival after stroke. IPC seems also likely to be effective in other medical groups of patients at high risk of DVT.

Panel: Research in context

Systematic review

In stroke, results from large randomised trials had shown that prophylactic heparin/low molecular weight heparin (LMWH) had no net benefit and that graduated compression stockings did not reduce the risk of DVT. The CLOTS 3 trial aimed to establish whether intermittent pneumatic compression (IPC) reduced the risk of deep vein thrombosis (DVT) in patients admitted to hospital after an acute stroke who were initially immobile. Before starting the trial, we searched for other trials that had addressed this question in stroke patients. We updated this search in March, 2013. We searched the Cochrane Stroke Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (1966 to March 2013), Embase (1980 to March, 2013), CINAHL (1982 to March, 2013) and The British Nursing Index (1985 to March, 2013) using the search terms listed in the appendix. We screened reference lists of all relevant papers, searched ongoing trials registers (March, 2013), and contacted experts in the field. We included unconfounded randomised controlled trials comparing IPC for reducing the risk of DVT with control and in which prophylaxis was started within 7 days of the onset of stroke.

We identified two small trials of IPC, one including 151 patients with haemorrhagic stroke and the other 26 patients with unspecified stroke. When the results of CLOTS 3 are meta-analysed with the results of the two other trials, the estimates of treatment effects are an OR of 0·66 (95% CI 0·52–0·84) for proximal DVT, an OR of 0·71 (0·59–0·85) for any DVT, and an OR of 0·81 (0·65–1·01) for deaths by the end of the treatment period. The two other trials did not report any symptomatic DVTs or pulmonary emboli.

The overall rate of proximal DVT in the CLOTS 3 trial was 10·3% (296 of 2876 patients), almost identical to that reported in CLOTS 1[3] (thigh-length graduated compression stockings *vs* none; 10·3% [259 of 2518 patients]), but higher than that in CLOTS 2[4] (thigh-length graduated compression stockings *vs* below-knee; 7·6% [236 of 3114 patients]). The death rates at 30 days were 12·0% (345 of 2876 patients) in CLOTS 3, 9·2% (232 of 2518 patients) in CLOTS 2,[4] and 11·4% (356 of 3114 patients) in CLOTS 1.[3] In CLOTS 3, 62·2% (1790 of 2876) of patients enrolled had a probability of a good outcome of 0–0·15 (ie, severe stroke; table 1), while the equivalent figures were 53·4% (1344 of 2518) in CLOTS 1[3] and 54·3% (1690 of 3114) in CLOTS 2.[4] In all three trials, early screening CDU was performed in about 91% of enrolled patients, whilst in CLOTS 3 the second CDU was done in 65·7% (1890 of 2876) compared with only 57·8% (1456 of 2518) in CLOTS 1[3] and 41·2% (1282 of 3114) in CLOTS 2.[4] Since patients in CLOTS 3 had more severe strokes, and were more intensively screened for DVT, one would have expected higher DVT and death rate—however this may in part have been offset by 50% of the patients in CLOTS 3 receiving effective prophylaxis for venous thromboembolism with IPC.

Interpretation

The CLOTS 3 data provide robust evidence for the effectiveness of IPC in the prevention of DVT and it possibly improves survival in patients who are initially immobile (ie, cannot walk to the toilet without the help of another person) after being hospitalised with acute stroke.

Contributors
See appendix.

Conflicts of interest
None of the writing committee had any conflicts of interest. However, the trial was reliant on donation of IPC by Covidien.

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For the **HTA programme website** see http://www.hta.ac.uk/project/2231.asp/

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